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10/565,273	01/20/2006	Naoyuki Katayama	081356-0255	5238

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EXAMINER	
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ART UNIT	PAPER NUMBER
1651	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/565,273	KATAYAMA ET AL.	
	Examiner	Art Unit	
	Lora E. Barnhart	1651	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *16 May 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-11 and 14-28* is/are pending in the application.

4a) Of the above claim(s) *14-24* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-11 and 25-28* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *11/13/07, 1/20/06*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Response to Amendments

Applicant's amendments filed 5/16/08 to the claims have been entered. Claims 12 and 13 have been cancelled. No claims have been added. Claims 1-11 and 14-28 remain pending in the current application.

Election/Restrictions

Applicant's election of Group I, claims 1-11 and 25-28, in the reply filed on 5/16/08 is acknowledged. Because applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (MPEP § 818.03(a)).

Claims 14-24 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected invention, there being no allowable generic or linking claim. Election was made **without** traverse in the reply filed on 5/16/08.

Applicant's election of the species "suppression of cancers" as in claim 26 in the reply filed on 5/16/08 is acknowledged. Because applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (MPEP § 818.03(a)).

Examination on the merits will commence on claims 1-11 and 25-28 ONLY, to the extent they read on the elected species where applicable.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the

art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-11 and 25-28 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method for preparing a Langerhans cell comprising contacting peripheral blood mononuclear cells (PBMCs) containing CD14+ monocytes with Delta-1, does not reasonably provide enablement for preparing a Langerhans cell from a population of PBMCs that lack CD14+ cells or from any population of PBMCs using any Notch ligand other than Delta-1. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

The factors to be considered in determining whether undue experimentation is required are summarized in *In re Wands*, 858 F.2d 731, 737, 8 USPQd 1400, 1404 (Fed. Cir. 1988) (a) the breadth of the claims; (b) the nature of the invention; (c) the state of the prior art; (d) the level of one of ordinary skill; (e) the level of predictability in the art; (f) the amount of direction provided by the inventor; (g) the existence of working examples; and (h) the quantity of experimentation needed to make or use the invention based on the content of the disclosure. While all of these factors are considered, a sufficient number are discussed below so as to create a *prima facie* case.

The cited claims are drawn broadly to a method of differentiating PBMCs by contacting them with any Notch ligand; claims 6 and 27 list several Notch ligands, including four forms of Delta and two forms of Jagged. The specification includes working examples and specific guidance only for the embodiment in which the Notch

ligand is Delta-1 and for which the PBMC population includes CD14+ cells. This level of guidance is insufficient given the state of the art, which will be discussed below.

While both Delta and Jagged are receptors for Notch, their effects on cells are diverse. Jaleco et al. (2001, *Journal of Experimental Medicine* 194: 991-1002; reference V) teach that Delta-1 and Jagged-1 have very different effects on the cell fate decision of hematopoietic stem cells (HSCs); culturing HSCs with cells expressing Delta-1 inhibited differentiation along the B cell pathway, while culturing HSCs with cells expressing Jagged-1 produced no such block (page 996, column 1). Delta-1 and Jagged-1 also had differential effects on gene expression in HSCs (Table I at page 995), indicating that the these Notch ligands are not interchangeable in the development of hematopoietic lineages.

Work published after the instant application was filed indicates that determining the effect Delta or Jagged might have on various cells would have required undue experimentation at the time of the invention. Neves et al. (2006, *Stem Cells* 24: 1328-1337; reference W) verify Jaleco's observation that Delta and Jagged have different effects on HSCs (page 1330, column 2, e.g.) and that the mechanisms underlying the differences are still not known (page 1329, column 1, and page 1336). Tohda et al. (2005, *Experimental Hematology* 33: 558-563; reference X) concur that the mechanism underlying the different effects of Delta and Jagged on hematopoietic cells is unknown (page 563, column 1). No explanation for the differences among the Notch ligands' effects on cells is known years after the instant invention; therefore, predicting the

effects of a given Notch ligand on a given cell could not be considered routine experimentation at the time of the invention.

Only claim 8 requires that the PBMC population contain CD14+ cells; however, the art suggests that only CD14+ cells can give rise to Langerhans cells. Geissmann (1998, *Journal of Experimental Medicine* 187: 961-966; reference U) teaches that Langerhans cells arise from CD14+ monocytes (page 961). Jaksits et al. (1999, *Journal of Immunology* 163: 4869-4877; reference U2) concur that Langerhans cells arise in culture from CD14+ cells (page 4869). Indeed, applicants' own work, published after the instant filing (Hoshino et al., *Journal of Leukocyte Biology* 78: 921-929; reference V2) indicates that CD14+ cells are an essential component of the starting PBMC to yield Langerhans cells (page 922, column 1).

Applicants present a single working embodiment in which CD14+ PBMC (page 7, last paragraph, e.g.) are cultured in a plate on which Delta-1 has been immobilized (page 20, paragraph 2; and page 27, paragraph 2, e.g.). The specification provides no guidance for producing Langerhans cells from a PBMC population that does not include CD14+ cells or for producing Langerhans cells using any Notch ligand other than Delta-1. M.P.E.P. § 2164.03 reads, "The amount of guidance or direction needed to enable the invention is inversely related to the amount of knowledge in the state of the art as well as the predictability in the art. *In re Fisher*, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970). The 'amount of guidance or direction' refers to that information in the application, as originally filed, that teaches exactly how to make or use the invention. The more that is known in the prior art about the nature of the invention, how to make,

and how to use the invention, and the more predictable the art is, the less information needs to be explicitly stated in the specification. **In contrast, if little is known in the prior art about the nature of the invention and the art is unpredictable, the specification would need more detail as to how to make and use the invention in order to be enabling.** See, *e.g., Chiron Corp. v. Genentech Inc.*, 363 F.3d 1247, 1254, 70 USPQ2d 1321, 1326 (Fed. Cir. 2004)...In applications directed to inventions in arts where the results are unpredictable, the disclosure of a single species usually does not provide an adequate basis to support generic claims. In cases involving unpredictable factors, such as most chemical reactions and physiological activity, more may be required." As the above discussion illustrates, the effects of Notch ligands on hematopoietic cells were unpredictable at the time of the invention, as was the potential to yield Langerhans cells from PBMC populations lacking CD14+ cells, so designing such methods must be considered "nascent," and the amount of guidance required is relatively high.

While a singular, narrow working embodiment cannot be a sole factor in determining enablement, its limited showing, in light of the unpredictable nature of the art and the lack of direction applicants present, provides additional weight to the lack of enablement in consideration of the *Wands* factors as a whole. Thus, one of ordinary skill in the art would not have a reasonable expectation of success in using the claimed invention across its entire scope. A claim in which both the Notch ligand is particularly limited to Delta-1 **and** the PBMC necessarily is CD14+ would not be subject to this ground of rejection.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 25-28 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 25-28 provides for a method of making Langerhans cells that may then be used in various therapeutic methods, but, since the claim does not set forth any steps involved in the therapeutic methods, it is unclear what method/process applicant is intending to encompass. A claim is indefinite where it merely recites a use without any active, positive steps delimiting how this use is actually practiced.

Claim Rejections - 35 USC § 101

35 U.S.C. 101 reads as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

Claims 25-28 are rejected under 35 U.S.C. 101 because the claimed recitation of a use, without setting forth any steps involved in the process, results in an improper definition of a process, i.e., results in a claim which is not a proper process claim under 35 U.S.C. 101. See for example *Ex parte Dunki*, 153 USPQ 678 (Bd.App. 1967) and *Clinical Products, Ltd.* v. *Brenner*, 255 F. Supp. 131, 149 USPQ 475 (D.D.C. 1966). Claims 25-28 are drawn to methods of making cells "used for" various treatments, but there are no steps within these treatments.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1-8, 11, and 25-28 are rejected under 35 U.S.C. 103(a) as being unpatentable over Geissmann et al. (1998, *Journal of Experimental Medicine* 187: 961-966; reference U) taken in view of Ohishi et al. (2001, *Blood* 98: 1403-1407; reference B3 on 11/13/07 IDS). This rejection pertains to the embodiment in which the Notch ligand is Delta-1; the peripheral blood mononuclear cell is a CD14+ monocyte; and the agent added in claim 11 is TNF-alpha.

Geissmann teaches isolating CD14+ monocytes from human peripheral blood mononuclear cells (page 961, column 2) and culturing them in a differentiation medium comprising GM-CSF and TGF-beta (page 962, column 1). Geissmann teaches that

CD14+ monocytes so cultured generate dendritic-shaped cells that are identified as Langerhans cells by their staining for Lag antigen (page 962, column 2). The Langerhans cells yielded by the method of Geissmann express E-cadherin (ibid.). Geissmann teaches adding TNF-alpha to the differentiation medium to promote maturation of their Langerhans cells (page 963, column 2).

Geissmann does not teach including a Notch ligand in their differentiation medium.

Ohishi teaches coating a 96-well plate with antibodies to c-myc, then adding a fusion protein containing Delta-1 (a Notch ligand) attached to 6 myc tags to immobilize Delta-myc on the plate (page 1403). Ohishi teaches culturing isolated human monocytes in these coated wells in medium containing GM-CSF (page 1403, second column, and page 14, first column). Ohishi teaches that monocytes so cultured differentiate into dendritic cells (pages 1404-1405).

The prior art indicates that GM-CSF (Geissmann and Ohishi), TGF-beta (Geissmann), and Delta-1 (Ohishi) promote differentiation along the dendritic cell pathway in monocytes, particularly in CD14+ monocytes; all three of these factors have the same effect on CD14+ monocytes. "It is *prima facie* obvious to combine two compositions each of which is taught by the prior art to be useful for the same purpose, in order to form a third composition to be used for the very same purpose.... [T]he idea of combining them flows logically from their having been individually taught in the prior art." *In re Kerkhoven*, 626 F.2d 846, 850, 205 USPQ 1069, 1072 (CCPA 1980) (citations omitted). See M.P.E.P. § 2144.06. A person of ordinary skill in the art would have had a

reasonable expectation of success in conducting the culturing of Geissmann in the Delta-1-coated plates of Ohishi to produce Langerhans cells (which are one type of dendritic cells) because Geissmann and Ohishi teach that GM-CSF, TGF-beta, and Delta-1 all promote differentiation of CD14+ monocytes along this pathway.

Claims 25-28 are included in this rejection because, as discussed above, they do not distinctly further limit the method of claims 1-8 and 11, since no particular method steps are included in the "used for" limitations. In any case, M.P.E.P. § 2111.02 reads, "If the body of a claim fully and intrinsically sets forth all of the limitations of the claimed invention, and the preamble merely states, for example, the purpose or intended use of the invention, rather than any distinct definition of any of the claimed invention's limitations, then the preamble is not considered a limitation and is of no significance to claim construction." As such, the limitation "for suppression of cancers," e.g., does not affect the patentability of the claimed composition/method. Compositions are defined by their physical, structural, and chemical properties, not by an intended use or application. Methods are defined by their constituent steps, not by an intended use or application.

Therefore, the invention as a whole would have been *prima facie* obvious to a person of ordinary skill at the time the invention was made.

Claims 9 and 10 are rejected under 35 U.S.C. 103(a) as being unpatentable over Geissmann taken in view of Ohishi as applied to claims 1-8 and 25-28 above, and further in view of Steinman et al. (1999, U.S. Patent 5,994,126; reference A) and Banchereau et al. (2004, U.S. Patent Application Publication 2004/0022761; reference

B). This rejection pertains to the embodiment in which the Notch ligand is Delta-1; the peripheral blood mononuclear cell is a CD14+ monocyte; and the agent added in claim 11 is TNF-alpha.

The teachings of Geissmann and Ohishi are relied upon as above. Geissmann and Ohishi do not teach that Langerhans cells made by their methods express all of the markers recited in claims 9 and 10.

Steinman teaches that Langerhans cells express HLA-ABC, HLA-DR, CD80, and CD86 (column 12, lines 28-42).

Banchereau teaches that langerin is a marker of Langerhans cells and that these cells also express CCR6 (paragraph 19).

A person of ordinary skill in the art would have had a reasonable expectation that the Langerhans cells yielded by the method of Geissmann in view of Ohishi express langerin, CCR6, HLA-ABC, HLA-DR, CD80, and CD86 as in claims 9 and 10 because Geissmann teaches that their Langerhans cells are bona fide Langerhans cells that express E-cadherin and have the morphology of Langerhans cells (page 962, column 2, through page 963, column 2). Furthermore, Ohishi teaches that the cells yielded by their methods have adopted dendritic cell fate (page 1405 and Figure 3D).

It would therefore have been obvious to a person of ordinary skill in the art at the time the invention was made to use the method of Geissmann in view of Ohishi to make Langerhans cells expressing the markers in claims 9 and 10 because Geissmann and Ohishi teach that their methods produce Langerhans cells (a specialized type of

dendritic cell); therefore, the skilled artisan would have expected that cells made by these methods possess all of the inherent properties of Langerhans cells.

Therefore, the invention as a whole would have been *prima facie* obvious to a person of ordinary skill at the time the invention was made.

Claim 11 is rejected under 35 U.S.C. 103(a) as being unpatentable over Geissmann in view of Ohishi and, as necessary, Steinman and Banchereau, as applied to claims 1-10 and 25-28 above, and further in view of Vicari et al. (2002, U.S. Patent Application Publication 2002/0034494; reference C). This rejection pertains to the embodiment in which the Notch ligand is Delta-1; the peripheral blood mononuclear cell is a CD14+ monocyte; and the agent added in claim 11 is CD40 ligand or LPS.

The teachings of Geissmann, Ohishi, Steinman, and Banchereau are relied upon as discussed above. None of Geissmann, Ohishi, Steinman, and Banchereau teaches adding CD40 ligand or LPS to Langerhans cells.

Vicari teaches that CD40 ligand, TNF-alpha, and LPS were known in the art at the time of the invention to promote maturation of dendritic cells (paragraph 62).

A person of ordinary skill in the art would have had a reasonable expectation of success in adding CD40 ligand or LPS in place of the TNF-alpha used by Geissmann because Vicari teaches that these three components are functional equivalents, i.e. that they all promote maturation of dendritic cells. The skilled artisan would have been motivated to include at least one of these components because both Geissmann and Vicari teach that they lead to mature dendritic cells.

It would therefore have been obvious to a person of ordinary skill in the art at the time the invention was made to add any combination of CD40 ligand, TNF-alpha, and LPS to the Langerhans cells of Geissmann taken in view of Ohishi, Steinman, and Banchereau because Geissmann and Vicari teach that these agents promote maturation of dendritic cells.

Therefore, the invention as a whole would have been *prima facie* obvious to a person of ordinary skill at the time the invention was made.

No claims are allowed. No claims are free of the art.

Applicant is requested to specifically point out the support for any amendments made to the disclosure in response to this Office action, including the claims (MPEP 714.02 and 2163.06). In doing so, applicant is requested to refer to pages and line numbers in the as-filed specification, **not** the published application. Due to the procedure outlined in MPEP § 2163.06 for interpreting claims, it is noted that other art may be applicable under 35 U.S.C. § 102 or 35 U.S.C. § 103(a) once the aforementioned issue(s) is/are addressed.

Applicant is requested to provide a list of all copending U.S. applications that set forth similar subject matter to the present claims. A copy of such copending claims is requested in response to this Office action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Lora E. Barnhart whose telephone number is 571-272-1928. The examiner can normally be reached on Monday-Thursday, 9:00am - 5:30pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Michael G. Wityshyn can be reached on 571-272-0926. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Lora E Barnhart/
Primary Examiner, Art Unit 1651